Impact of regulatory interventions to restrict the combined use of renin-angiotensin system-acting agents in Denmark: interrupted time series analysis

PASS information

Title	Impact of regulatory interventions to restrict the combined use of renin-angiotensin system-acting agents in Denmark: interrupted time series analysis.
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Active substance	Angiotensin-converting enzyme inhibitor (ACEi) - ATC C09A and C09B. Angiotensin II receptor blocker (ARB) - C09C and C09D.
Medicinal product	N/A
Product reference	N/A
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Joint PASS	No

Research question and objectives	Research question Did co-prescribing of two different RAS-acting agents (also known as dual blockade) decrease in Denmark after the EMA referral on RAS-acting agents in 2014? Primary objective To assess the impact of the EMA referral procedure on the co-prescribing of RAS-acting agents by examining the trends in co-dispensing of ACEis and ARBs in Denmark. Secondary objectives To describe the population in terms of demographics (age and sex) co-prescribed an ACEi and an ARB over time.
Country of study	Denmark
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1. List of abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
ITS	Interrupted time series
PRAC	Pharmacovigilance Risk Assessment Committee
RAS	Renin-angiotensin-system

2. Responsible parties

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3. Abstract

Title Impact of regulatory interventions to restrict the combined use of renin-angiotensin system (RAS)-acting agents in Denmark: interrupted time series analysis, version 1.0, December 2020.

Rationale and background: Through a referral procedure in 2014, the European Medicines Agency recommended risk minimisation measures, including restrictions on the combined use of RAS-acting agents. Evaluation of risk minimisation measures is an integral part of risk management, and it is essential to ensure that the benefits of a particular medicinal product exceed the risks by the greatest achievable margin.

Research question: Did co-prescribing of two different RAS-acting agents (also known as dual blockade) decrease in Denmark after the EMA referral on RAS-acting agents in 2014?

Objectives: The primary objective of this study was to assess the impact of the EMA referral on the co-prescribing of RAS-acting agents in Denmark by examining the trends in co-dispensing of Angiotensin-converting enzyme inhibitors (ACEis) and Angiotensin II receptor blockers (ARBs). A secondary objective was to describe the population in terms of demographics (age and sex) co-prescribed an ACEi and an ARB over time.

Study design: This is a descriptive drug utilisation study using an interrupted time series design based on pharmacy dispensing data of RAS-acting agents.

Population: The source population was derived from the population of Denmark (~5.8 million): those who picked up a prescription for an ARB or ACEi from a community pharmacy between 1 January 2008 and 31 December 2018 and were ≥18 years old.

Variables: Each of the class of drugs acting on the RAS has been identified with the following WHO ATC codes:

- ACEis: C09A, C09B,
- ARBs: C09C, C09D.

Based on dispensing dates falling within a specific month, the primary outcome variable was:

- Monthly prevalence of patients co-dispensed an ARB and an ACEi on the same day per 1,000,000 population.

Data sources: The study included nationwide secondary data from the National Prescription Registry (NPR) covering all prescriptions dispensed by community pharmacies in Denmark.

Study size: This study is a descriptive analysis of the whole Danish population. No sample size or statistical precision calculation was performed.

Data analysis: We used autoregressive integrated moving average (ARIMA) interrupted time series regression model as outlined by the Cochrane Effective Practice and Organisation of Care (EPOC) to evaluate the change in dispensing trends from pre-intervention to post-intervention. A linear regression model of the monthly prevalence of co-medication of ACEis and ARBs was used. We used 24 data points before and 24 data points after the intervention and aimed for a minimum of 100 observations at each data point.

4. Amendments and updates

None.

5. Rationale and background

Renin–angiotensin system (RAS) agents (also called RAS blockers) act by blocking different stages of the RAS, which is a hormone system regulating blood pressure, systemic vascular resistance, and fluid and electrolyte balance. RAS-agents include angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs) and direct renin inhibitors such as aliskiren. They are used to treat hypertension, heart failure, and diabetic nephropathy [1]. Dual RAS blockade therapy (combination therapy with different RAS-acting agents) emerged in the late 1990s based on improvements in surrogate endpoints (e.g., blood

pressure and proteinuria). Despite a lack of solid evidence, it was commonly used in patients with hypertension and with diabetes or proteinuria or both, as well as in those with heart failure [2]. However, since then, several publications have raised concerns regarding dual blockade therapy through the combined use of ACEis, ARBs, or aliskiren. In 2003, the Valsartan in Acute Myocardial Infarction Trial (VALIANT) demonstrated an increase of adverse events without improving survival among patients prescribed combination therapy who are at high risk for cardiovascular events after myocardial infarction [3]. In 2008, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), which recruited patients with high-risk vascular events, showed no significant benefit of combination therapy on efficacy, but there was an increased frequency of hyperkalaemia, hypotension, syncope, and acute dialysis when combining an ACEi and an ARB [4]. Also, in 2008, a meta-analysis showed excess risk coupled with a lack of consistent mortality benefit for left ventricular dysfunction with combination therapy compared with ACEi alone [5]. The emerging evidence was subsequently reflected in the UK NICE guideline from 2011 [6], where co-prescribing of ACEis and ARBs is contra-indicated; as well as in the therapeutic guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) from 2013 [7], where co-prescription is not recommended.

In May 2013, the European Medicines Agency (EMA) started a review (referral procedure, Article 31 of Directive 2001/83/EC) of the risks of combining RAS-acting agents in the treatment of hypertension and congestive heart failure. This led to the Pharmacovigilance Risk Assessment Committee (PRAC) recommending risk minimisation measures (RMMs) in April 2014, including restrictions of the combined use of RAS-acting agents [8]. These recommendations were based on a detailed review of the available data, including large clinical trials and meta-analyses [2,4,9,10], which conclusively demonstrated that dual RAS blockade is associated with an increased risk of hypotension, hyperkalaemia, and renal failure compared to monotherapy. Furthermore, no significant benefits from dual blockade were seen in patients without heart failure. The review of evidence in 2013/2014 by the PRAC relating to all RAS-acting agents supported a previous EMA review relating specifically to medicines containing aliskiren. The results of the review on aliskiren were communicated in February 2012 and concluded [11]:

- Aliskiren is contraindicated in patients with diabetes (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73 m^2) who take ACEis or ARBs;
- The combination of aliskiren and ACEi or ARB is not recommended in all other patients.

In addition to confirming the previous review on aliskiren, the PRAC recommendations in 2014 [8], expanded the warning of combination therapy to include any combination of RAS-acting agents, that is, also the combination of ACEis and ARBs:

- Combined use of ACEis and ARBs is not recommended in any patient. In particular, ACEis and ARBs should not be used concomitantly in patients with diabetic nephropathy.

As the concerns regarding the lack of efficacy and the adverse events identified in association with dual RAS blockade therapy were considered to be class effects, the data was relevant to all ACEis and ARBs. However, excluding products containing candesartan and valsartan, ARBs, which are also authorised in the treatment of heart failure, an exception was made. Additional information was agreed upon to reflect the fact that the available data suggests that

- The ARBs valsartan and candesartan remain authorised for treatment of heart failure in combination with ACEis in selected patients who cannot use other heart failure treatments.

Considering the communication in 2012 on aliskiren, we anticipated that the main impact of the RMM in 2014 is a reduction of co-prescribing of ACEis and ARBs. According to a study conducted by the EMA investigating co-prescribing of RAS blockers in France, Germany, and the UK during 2001—2012, the recommendations from EMA in early 2012 may have been effective to avoid co-prescription with aliskiren [6]. Furthermore, aliskiren lost its general reimbursement status in Denmark in November 2010, and according to the Danish Society of Cardiology, aliskiren is rarely used [12]. Hence, the scope of the current study was on the co-prescription of ACEis and ARBs only.

Other studies investigating co-prescribing of RAS blockers include

- a study in the Irish population from 2000 to 2009 observed an increase in co-prescribing of ACEIs and ARBs, but prescribing patterns did not appear to be affected by results from major trials [13];
- a study in Puerto Rico found that ACEi and ARB co-prescribing during the years 2012 and 2013 was frequently prescribed in patients with diagnoses for which the combination is not clinically indicated [14], and
- a study in the UK assessed the impact of the regulatory action taken in 2014 on the co-prescribing of renin-angiotensin by issuing prescriptions between 2009 through June 2015 found that co-prescribing declined in line with recommendations. There was, however, a decreasing trend before this, likely due in part to prior publication of the data used in the EU review [15].

Evaluation of RMM is an integral part of risk management and evidence of risk minimisation program effectiveness is critical for demonstrating that the benefits of a particular medicinal product exceed the risks by the greatest achievable margin [16]. So far, research on the impact of the regulatory intervention in 2014 has been conducted only in the UK [17]. To date, no studies have been conducted in Denmark.

6. Research question and objectives

6.1. Research question

Did co-prescribing of two different RAS-acting agents (also known as dual blockade) decrease in Denmark after the EMA referral on RAS-acting agents in 2014?

6.2. Primary objective

The primary objective of this study was to assess the impact of the EMA referral procedure on the co-prescribing of RAS-acting agents by examining the trends in co-dispensing of ACEis and ARBs in Denmark.

6.3. Secondary objective

A secondary objective of this study was to describe the population in terms of demographics (age and sex) co-prescribed an ACEi and an ARB over time.

7. Research methods

7.1. Study design

This is a descriptive drug utilisation study using an interrupted time series design based on pharmacy dispensing data of RAS-acting agents.

7.2. Study population

The source population was derived from the population of Denmark (~5.8 million): those who picked up a prescription for an ARB or ACEi from a community pharmacy between 1 January 2008 and 31 December 2018 and were ≥18 years old.

7.3. Setting and data sources

The study included nationwide secondary data from the National Prescription Registry (NPR) covering all prescriptions dispensed by community pharmacies in Denmark [18].

7.4. Variables

The following classes of drugs acting on the RAS have been included: Angiotensin II receptor blockers (ARBs) and Angiotensin-converting enzyme inhibitors (ACEis).

Each of the class has been identified with the following WHO ATC codes:

- ACEis: C09A, C09B.
- ARBs: C09C, C09D.

7.4.1. Outcome variables

Monthly co-prescribing was defined as an ACEi and an ARB dispensed the same day based on dispensing dates falling within a specific month. We calculated monthly prevalence rate of co-dispensing from 1 January 2008 to 31 December 2018 by dividing the number of patients with at least one co-dispensing within a month by the number of the total population (≥18 years old) in Denmark.

Outcome variables used to examine trends in co-dispensing of ACEis and ARBs:

- Monthly prevalence of patients co-dispensed an ARB and an ACEi on the same day per 1,000,000 population;
- Monthly prevalence of patients co-dispensed an ARB and an ACEi among patients dispensed an ARB or an ACEi or both.

7.4.2. Other variables

The outcomes were stratified according to

- Sex,
- Age groups:
    - 18–64,
    - ≥65 years old.

7.5. Study size

This study is a descriptive analysis of the whole Danish population. No sample size or statistical precision calculation was performed.

7.6. Data management

Stata software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) was used to manage the data on the remote servers of Statistics Denmark and to create tables with monthly rates.

7.7. Data analysis

We used autoregressive integrated moving average (ARIMA) interrupted time series regression model as outlined by the Cochrane Effective Practice and Organisation of Care (EPOC) to evaluate change in dispensing trends from pre-intervention to post-intervention [19]. ARIMA models are well established in the literature on drug utilisation research [20,21]. We used a linear regression model of the monthly prevalence of co-prescription of ACEis and ARBs. The linear trend was assessed by visual inspection of the pre-intervention data [22], and homogeneity of variance and normal distribution of residuals was used to check the assumptions of the linear regression model [23].

Two parameters define each segment of a time series: level and trend. A change in slope is expected where interventions have a gradual roll-out resulting in a gradual intervention effect [20]. In contrast, a change in level, for example, a drop in the outcome after the intervention, constitutes an abrupt intervention effect [23]. A priori we hypothesised that the intervention (RMMs) would decrease co-dispensing of ACEis and ARBs. Since the intervention was a warning about combination therapy and not a full contraindication and the update of the product information was not accompanied by direct communication to healthcare professionals, we assumed that the main effect was merely a gradual effect than an abrupt effect. Furthermore, in accordance with a study from the UK, we expected that the regression line would flatten at the end of the study period approaching a small constant prevalence indicating that clinicians may still co-prescribe combination therapy if considered absolutely necessary [17].

We used regression modelling to evaluate these three ITS components [22]:

1. The slope before the intervention time point with 95% confidence intervals (CIs) and P values,
2. The change in slope from pre-intervention to post-intervention with 95% confidence intervals (CIs) and P values for the null hypothesis that the slopes are the same,
3. The change in the level of co-dispensing between the time points immediately before and immediately after the intervention with 95% confidence intervals (CIs) and P values.

A sufficient number of time points and observations at each data point is needed to conduct segmented regression analysis. To evaluate autocorrelation adequately, we used 24 data points before and 24 data points after the intervention and aimed for a minimum of 100 observation at each data point [23].

Periods were defined as follows.

- The pre-intervention period was defined as 24 months before the PRAC recommendation in April 2014, that is, from May 2012 to April 2014.
- The date of the regulatory intervention was pre-specified as the date of the PRAC recommendation in April 2014.
- The post-intervention period was defined as May 2014 to April 2016.

Summary statistics were undertaken to identify seasonal patterns. The Durbin–Watson statistic was used to test for autocorrelation [23], and the Dicky-Fuller test was used for non-stationarity [21].

Analyses were performed in R.

7.7.1. Sub-groups

Co-prescription of ARBs was stratified according to whether they were indicated for the treatment of heart failure in combination with ACE-inhibitors:

- Valsartan + candesartan: C09CA03, C09CA06, C09DA03, C09DA06, C09DB01, C09DB07, C09DB08, C09DX01, C09DX04, C09DX05, C09DX06, C10BX10;
- Other ABRs: C09C and C09D except for codes listed under valsartan or candesartan.

7.7.2. Sensitivity analysis

The following sensitivity analyses were carried out.

- We tested whether our results changed when using 12 data points before and 12 data points after the intervention.
- We tested whether our results changed when moving the intervention time 12 months back to the start of the referral procedure in June 2013.
- We tested whether our results changed when excluding products containing candesartan and valsartan.

- A pre-planned sensitivity analysis considered a 30-day and a 7-day time window. The date of the co-prescription was defined as the date of the second dispensing. This approach has been adopted by Tobi et al. [24], by Wan et al. who describe the co-prescribing trend of ACEis and ARBs in Ireland [13], by Allen and Donegan who investigated co-prescribing of RAS blockers in the UK [17], and by the EMA [6].
- A sensitivity analysis was performed by adding a lag period from April 2014 to October 2014, thereby moving the intervention date to October 2014. The lag period covered the time from the PRAC recommendation in April 2014 to four weeks after the European Commission's final decision in September 2014 where the public health communication is updated saying that the review is now final, and translations in all official EU languages are published.

7.8. Quality control

This protocol is consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices [25] and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [26]. The protocol underwent senior scientific review.

A different analyst independently reviewed all programming written by one study analyst, and two authors independently checked the accuracy and consistency for all data outputs and ATC code lists.

7.9. Limitations of the research methods

There were several limitations to this study.

- Since same-day co-dispensing was used, we might have underestimated the overall extent of co-prescription. However, using a wider definition of co-prescription might lead to misclassification of switching as co-prescription.
- Patients may be classified as exposed when they are not taking the drug. Adherence to the prescription by patients was outside the scope of the study.
- In-hospital use of medication was not captured in the study.
- The data did not allow the assignment of heart failure diagnosis, making it impossible to determine whether there was a possible indication for co-prescribing of ACEis and ARBs. This may cause an overestimation of inappropriate co-prescribing in this study.
- Although interrupted time series analysis is a robust quasi-experimental design to evaluate the effects of regulatory interventions, it examines associations around a pre-specified period, and prescribing behaviour may be affected by other factors co-occurring at other times.

- No established thresholds exist for a successful impact of regulatory interventions or, perhaps more importantly, whether further regulatory action would be required to reinforce warnings and contraindications.

8. Ethical considerations and permissions

The Danish Data Protection Agency approved the study (514-0301/19-3000). Register-based studies do not require approval from an ethics review board [27].

9. Plans for disseminating and communicating study results

The study is planned to be registered in the ENCePP E-Register of Studies.

Study results will be considered for publication and will follow the International Committee of Medical Journal Editors (ICMJE 2015) guidelines. Also, communication in appropriate scientific meetings will be considered.

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Annex 1: timeline of important publications

Date	Organisation / journal	Outcome / action	Link
13/11/2003	NEJM	This clinical study demonstrated an increase in adverse events for patients prescribed combination therapy and no improvement in the survival rates for post myocardial infarction patients with heart failure [3].	
04/2008	Journal of Cardiac Failure	Meta-analysis of nine trials involving 18,160 patients, raised concerns about ACEI+ARB combination therapy compared with ACEI alone. The study showed excess risk, coupled with a lack of consistent mortality benefit for left ventricular dysfunction [5].	
10/04/2008	NEJM	Telmisartan (ARB) was equivalent to ramipril (ACEI) in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit [4].	
16/08/2008	The Lancet	In people at high vascular risk, telmisartan's (ARB) effects on major renal outcomes are similar to ramipril (ACEI). Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes [28].	

Date	Organisation / journal	Outcome / action	Link
10/02/2009	Journal of the American College of Cardiology	This review strongly discouraged the use of dual ACEI and ARB therapy [29].	
05/2009	Canadian Hypertension Society	The Canadian Hypertension Society recommended that a combination of an ACEI and ARB be avoided in hypertensive patients without heart failure or proteinuria [13,30]	
25/08/2010	NICE	The NICE guideline on management of chronic heart failure in adults in primary and secondary care (2010) recommends to “Seek specialist advice before offering second-line treatment to patients with heart failure due to left ventricular systolic dysfunction”. Specialist advice is also recommended if considering combination therapy with an ARB for a patient remaining symptomatic despite optimal treatment with an ACE-inhibitor and a beta-blocker, especially if the patient has mild to moderate heart failure (NYHA class II-IV) [31].	
15/11/2010	DKMA	Aliskirin lose their general reimbursement status in Denmark [12].	No general reimbursement of aliskiren

Date	Organisation / journal	Outcome / action	Link
24/08/2011	NICE	In the UK NICE guidelines from 2011, co-prescribing of ACE and ARB is contra-indicated [6].	
12/2011	EMA	Review started on Aliskiren after termination of the ALTITUDE study. CHMP advised doctors that they should not prescribe aliskiren to diabetic patients in combination with ACE inhibitors or ARBs [11].	Press release on aliskiren
17/02/2012	EMA	Press release on contraindications and warnings for aliskiren-containing medicines. Combination of aliskiren with ACEIs and ARBs no longer recommended for patients; contraindications in patients with diabetes or kidney problems [11].	Press release on aliskiren
15/03/2012	DKMA	The newsletter Danish Pharmacovigilance Update publish contraindications and warnings for aliskiren-containing medicines [32].	Danish Pharmacovigilance Update publish EMA contraindications and warnings of aliskiren
05/2012	European Society of cardiology	The 2012 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure advises that “The addition of an ARB (or renin inhibitor) to the combination of an ACE-inhibitor AND a mineralocorticoid antagonist is NOT recommended because of the risk of renal dysfunction and hyperkalaemia” in patients with symptomatic (NYHA class II–IV) systolic heart failure [33].	

Date	Organisation / journal	Outcome / action	Link
03/11/2012	NEJM	The addition of aliskiren to RAS blockade in patients with type 2 diabetes is not supported and may even be harmful [10].	
28/01/2013	BMJ	Meta-analysis of 33 clinical studies involving over 68,000 patients, raised concerns that combining several RAS-acting agents may be associated with an increased risk of hyperkalaemia, hypotension and kidney failure, compared with the single use of one RAS-acting agent. In addition, using multiple RAS-acting agents may not be more beneficial than using a single RAS-acting agent in terms of reducing overall mortality [2].	
02/2013	Journal of Hypertension	This study examined the effects of addition of an ACE inhibitor (ramipril) to an ARB (telmisartan) in 9628 people with diabetes. The study highlighted concerns of dual RAS blockade therapy, reporting an increased risk of acute dialysis and hyperkalaemia in patients prescribed ACE-inhibitors and ARBs together [34].	
16/05/2013	EMA	RAS referral started [8].	Overview of referral on renin-angiotensin-system (RAS)-acting agents
06/2013	American College of Cardiology	The 2013 ACCF/AHA Guideline for the Management of Heart Failure advises that the combination treatment of	

Date	Organisation / journal	Outcome / action	Link
	Foundation / American Heart Association	ARBs and ACE-inhibitors can be used to treat heart failure with EF<40% (NHYA class II-IV) if there are still heart failure symptoms despite optimal standard therapy with ACE-inhibitors and beta-blockers, especially in patients for whom an aldosterone antagonist is not indicated or tolerated. It also advises that "the routine combined use of an ACE-inhibitor, ARB and aldosterone antagonist is potentially harmful" and is not recommended [35].	
21/07/2013	European Society of Hypertension (ESH) and European Society of Cardiology (ESC)	The 2013 ESH/ESC Guidelines for the management of arterial hypertension [7], specifies that "the only combination that cannot be recommended on the basis of trial results is that between two different blockers of the RAS". This recommendation is based on the results of ONTARGET and ALTITUDE studies [4,10,28]. The guideline further states that "The combination of two antagonists of the RAS is not recommended and should be discouraged".	
14/11/2013	NEJM	In October 2012, the data and safety monitoring committee recommended that the study treatment be stopped, primarily on account of safety concerns due to increased rates of serious adverse events, hyperkalaemia,	

Date	Organisation / journal	Outcome / action	Link
		and acute kidney injury in the combination-therapy group as compared with the monotherapy group. Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy [9].	
10/04/2014	EMA	PRAC RAS referral recommendation.	PRAC recommendation of referral on RAS-acting agents PRAC referral assessment report
23/05/2014	EMA	CHMP decision on RAS referral	CHMP decision on RAS referral
06/2014	DKMA	The newsletter Danish Pharmacovigilance Update publish contraindications and warnings of RAS-agents [36].	Danish Pharmacovigilance Update publish EMA contraindications and warnings of RAS-agents
04/09/2014	EMA	European Commission final decision on RAS referral.	Amendments to relevant sections of the SPC
2015	The Danish Hypertension Society	Guideline on hypertension: “ARBs should normally not be combined with ACE-I” [a warning of co-medication with ARB + ACEI was not stated in the previous guideline from 2009] [37].	

Annex 2: ENCePP Checklist for Study Protocols

Study title: Impact of regulatory interventions to restrict the combined use of renin-angiotensin system-acting agents in Denmark: interrupted time series analysis

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☒	☐	
1.1.2 End of data collection[2]	☐	☒	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☐	☒	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Sec. 5
2.1.2 The objective(s) of the study?	☒	☐	☐	Sec. 6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Sec. 7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	Sec. 7.7
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	Sec. 7.1

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Sec. 7.3
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	Sec. 7.4.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	Sec. 7.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	Sec. 7.2
	4.2.2 Age and sex	☒	☐	☐	Sec. 7.2
	4.2.3 Country of origin	☒	☐	☐	Sec. 7.2
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Sec. 7.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Sec. 7.4.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	Sec. 7.9
5.3	Is exposure categorised according to time windows?	☒	☐	☐	Sec. 7.4.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	Sec. 7.4.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Sec. 7.4.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	Sec. 7.4.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	Sec. 7.4.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	Sec. 7.4.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Sec. 7.4.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Sec. 7.4.1
9.1.3 Covariates and other characteristics?	☐	☒	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Sec. 7.4.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Sec. 7.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☒	☐	☐	Sec. 7.4.2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	Sec. 7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	Sec. 7.5
10.3 Are descriptive analyses included?	☒	☐	☐	Sec. 7.7
10.4 Are stratified analyses included?	☒	☐	☐	Sec. 7.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	Sec. 7.9
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	Sec. 7.9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Sec. 7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Sec. 7.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	Sec. 7.7
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	Sec. 8
13.3 Have data protection requirements been described?	☐	☐	☐	Sec. 8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Sec. 4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	Sec. 9
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Sec. 9

Comments:

Name of the main author of the protocol: Per Sindahl

Date: 22/12/2020

Signature: _____